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Chapter 32: Antimicrobial Regimen Selection

INTRODUCTION

- A systematic approach to the selection and evaluation of an antimicrobial regimen is provided in **Table 32-1**. An *empiric* antimicrobial regimen is begun before the offending organism is identified and sometimes before documentation of the presence of infection, whereas a *definitive* regimen is instituted when the causative organism is known.

TABLE 32-1

Systematic Approach for Selection of Antimicrobials

Confirm the presence of infection Careful history and physical examination Signs and symptoms Predisposing factors
Identification of the pathogen (see Pharmacotherapy textbook Chapter e131) Collection of infected material Stains Serologies Culture and sensitivity
Selection of presumptive therapy considering every infected site Host factors Drug factors
Monitor therapeutic response Clinical assessment Laboratory tests Assessment of therapeutic failure

CONFIRMING THE PRESENCE OF INFECTION

FEVER

- *Fever* is defined as a controlled elevation of body temperature above the average of 36.7°C–37°C (98°F–98.6°F) (measured orally) and is a manifestation of many disease states other than infection.
- Fever can be caused by many drugs, and drug-induced fever is defined as persistent fever in the absence of infection or other underlying condition. The fever must coincide temporally with the administration of the offending agent and disappear promptly upon its withdrawal, after

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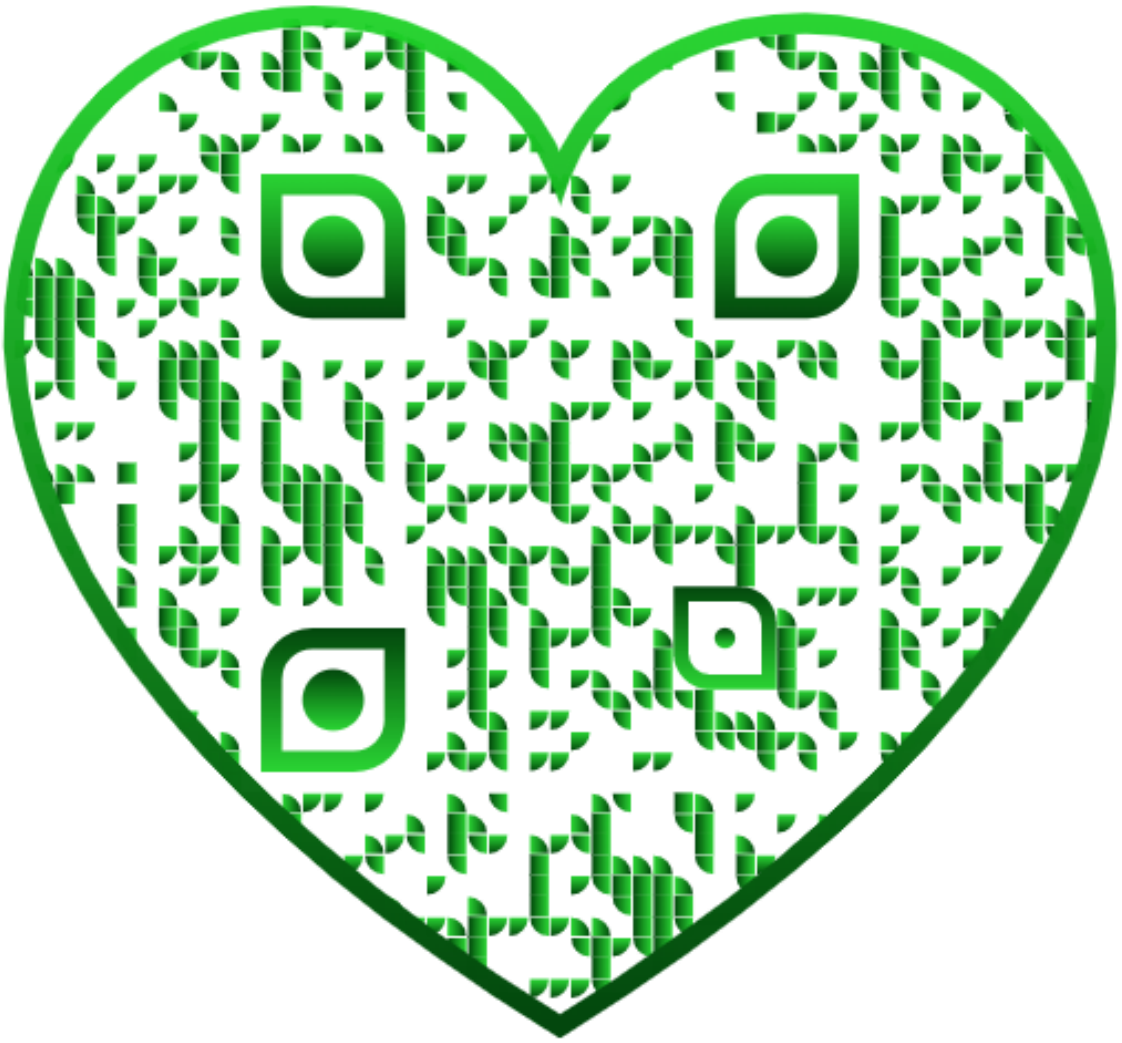

which the temperature remains normal.

WHITE BLOOD CELL COUNT

- Most infections result in elevated white blood cell (WBC) counts (leukocytosis) because of the mobilization of granulocytes and/or lymphocytes to destroy invading microbes. Normal values for WBC counts are between 4000 and 10,000 cells/mm^3 (4×10^9 and 10×10^9/L).
- Bacterial infections are associated with elevated granulocyte counts (neutrophils and basophils), often immature forms (band neutrophils) seen in peripheral blood smears. With infection, peripheral leukocyte counts may be high, but they are rarely higher than 30,000–40,000 cells/mm^3 (30×10^9/L to 40×10^9/L). Low neutrophil counts (neutropenia) after the onset of infection indicate an abnormal response and are generally associated with a poor prognosis for bacterial infection.
- Relative lymphocytosis, even with normal or slightly elevated total WBC counts, is generally associated with tuberculosis and viral or fungal infections. Many types of infections, however, may be accompanied by a completely normal WBC count and differential.

LOCAL SIGNS

- Pain and inflammation may accompany infection and are sometimes manifested by swelling, erythema, tenderness, and purulent drainage. Unfortunately, these signs may be apparent only if the infection is superficial or in a bone or joint.
- The manifestations of inflammation with deep-seated infections such as meningitis, pneumonia, endocarditis, and urinary tract infection must be ascertained by examining tissues or fluids. For example, the presence of polymorphonuclear leukocytes (neutrophils) in spinal fluid, lung secretions (sputum), and urine is highly suggestive of bacterial infection.

IDENTIFICATION OF THE PATHOGEN

- Identification and antimicrobial susceptibility of a suspected pathogen are the most important factors in determining the choice of antimicrobial therapy.
- Infected body materials must be sampled, if at all possible or practical, before the institution of antimicrobial therapy. A Gram stain of the material may reveal bacteria, or an acid-fast stain may detect mycobacteria or actinomycetes. Premature use of antimicrobials can suppress the growth of pathogens that might result in false-negative culture results or alterations in the cellular and chemical composition of infected fluids.
- Blood cultures should be performed in the acutely ill, febrile patient. Infected materials produced by the patient (eg, blood, sputum, urine, stool, and wound or sinus drainage) and less accessible fluids or tissues are obtained when needed to assess localized signs or symptoms. Abscesses and cellulitic areas should also be aspirated.
- After a positive Gram stain, culture results, or both are obtained, the clinician must be cautious in determining whether the organism recovered is a true pathogen, a contaminant, or a part of the normal flora. Cultures of specimens from purportedly infected sites that are obtained by sampling from or through contaminated areas might contain significant numbers of the normal flora.

SELECTION OF PRESUMPTIVE THERAPY

- Factors considered to select rational antimicrobial therapy for a given clinical situation include the severity and acuity of the disease, local epidemiology and antibiogram, patient history, host factors, factors related to the drugs used, and the necessity for using multiple agents. Choice of antimicrobial is influenced by local antimicrobial susceptibility data rather than information published by other institutions or national compilations.
- The drugs of choice for the treatment of most pathogens are compiled from a variety of sources and are intended as guidelines rather than specific rules for antimicrobial use (**Table 32-2**).
- Important considerations when selecting empiric antimicrobial therapy include: (1) prior knowledge of colonization or infections, (2) previous

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antimicrobial use, (3) the site of infection and the organisms most likely pathogens, and (4) local antibiogram and resistance patterns for important pathogens.

TABLE 32-2

Systematic Approach for Selection of Antimicrobials

Confirm the presence of infection Careful history and physical examination Signs and symptoms Predisposing factors
Identification of the pathogen (see Chapter e131 of DiPiro's Pharmacotherapy, 13th ed) Collection of infected material Stains Serologies Culture and sensitivity
Selection of presumptive therapy considering every infected site Host factors Drug factors
Monitor therapeutic response Clinical assessment Laboratory tests Assessment of therapeutic failure

HOST FACTORS

- When a patient for initial or empiric therapy is evaluated, the following factors should be considered:

  ✓ Allergy or history of adverse drug reactions.

  ✓ Age of patient.

  ✓ Pregnancy.

  ✓ Metabolic or genetic variation.

  ✓ *Renal and hepatic function*: Patients with diminished renal and/or hepatic function will accumulate certain drugs unless the dosage is adjusted.

  ✓ *Concomitant drug therapy*: Any concomitant therapy the patient is receiving may influence the selection of drug therapy, the dose, and monitoring. A list of selected drug interactions involving antimicrobials is provided in **Table 32-3**.

  ✓ Concomitant disease states.

TABLE 32-3

Major Drug-Drug Interactions with Antimicrobials

Antimicrobial	Interacting Agent(s)	Mechanism of Action/Effect	Clinical Management

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Aminoglycosides	Neuromuscular-blocking agents	Additive toxicity of neuromuscular-blocking agents	Monitor therapy
	Nephrotoxins (N) or ototoxins (O) (eg, amphotericin B [N], cisplatin [N/O], cyclosporine [N], furosemide [N/O], NSAIDs [N], radiocontrast [N], vancomycin [N/O])	Additive toxicity	Monitor renal function, obtain regular audiograms for patients receiving prolonged or repeated courses of aminoglycosides
	β-lactams	Aminoglycoside degradation	Separate administration and flush line thoroughly between doses of aminoglycoside and β-lactam therapy
Amphotericin B	Nephrotoxins (eg, aminoglycosides, cyclosporine, foscarnet)	Additive nephrotoxicity	Monitor renal function
Azoles	See Chapter 149 of DiPiro's Pharmacotherapy, 13th ed		
Foscarnet	Pentamidine IV	Increased risk of severe nephrotoxicity and hypocalcemia	Monitor renal function and serum calcium
Isoniazid	Carbamazepine, phenytoin	Decreased metabolism of carbamazepine and phenytoin, resulting in increased serum concentrations	Monitor for signs and symptoms of phenytoin and carbamazepine and phenytoin toxicity (eg, nausea, vomiting, nystagmus, ataxia)
Macrolides/azalides	Digoxin	Decreased digoxin bioavailability and metabolism	Monitor digoxin SDC
	Theophylline	Decreased metabolism of theophylline	Monitor theophylline SDC
Metronidazole	Ethanol (drugs containing ethanol)	Disulfiram-like reaction	Avoid
Fluoroquinolones	Other QTc-prolonging agents (eg, antiemetics, macrolides, azoles, antidepressants, etc)	Prolonged QTc interval	Monitor ECG at baseline and periodically while on concomitant QTc-prolonging therapy
	Multivalent cations	Decreased absorption of fluoroquinolone	Separate administration by at least 2 hours
Rifampin	Azoles, cyclosporine, methadone, propranolol, oral contraceptives, tacrolimus, warfarin	Increased of metabolism of interacting agent via rifampin induction of CYP-450 metabolism resulting in decreased serum concentrations	Avoid
Sulfonamides	Sulfonylureas, phenytoin, warfarin	Decreased metabolism of interacting agent resulting in increased serum concentrations	Monitor blood glucose, SDC of interacting agent, and PT
Doxycycline	Multivalent cations	Decreased absorption of tetracycline	Separate administration by at least 2

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			hours

ECG, electrocardiogram; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, prothrombin; SDC, serum drug concentration.

DRUG FACTORS

- Integration of both pharmacokinetic and pharmacodynamic properties of an agent is important when choosing antimicrobial therapy to ensure efficacy and prevent resistance. Antibiotics may demonstrate concentration-dependent (aminoglycosides and fluoroquinolones) or time-dependent (β-lactams) bactericidal effects.
- The importance of tissue penetration varies with the site of infection. The central nervous system (CNS) is one body site where the importance of antimicrobial penetration is relatively well defined, and correlations with clinical outcomes are established. Drugs that do not reach significant concentrations in cerebrospinal fluid should either be avoided or instilled directly when treating meningitis.
- Apart from the bloodstream, other body fluids in which drug concentration data are clinically relevant are cerebrospinal fluid, urine, ocular, synovial fluid, and peritoneal fluid.
- Pharmacokinetic parameters such as area under the drug concentration–time curve (AUC) and maximal observed concentration (peak) can be predictive of treatment outcome when specific ratios of AUC or maximal plasma concentration to the minimum inhibitory concentration (MIC) are achieved. For some agents, the ratio of AUC to minimum inhibitory concentration (MIC), peak:MIC ratio, or the time that the drug concentration is above the MIC (T > MIC) may predict efficacy.
- The most important pharmacodynamic relationship for antimicrobials that display time-dependent bactericidal effects (such as penicillins and cephalosporins) is the duration that drug concentrations exceed the MIC.

COMBINATION ANTIMICROBIAL THERAPY

- Combinations of antimicrobials are generally used to broaden the spectrum of coverage for empiric therapy, achieve synergistic activity against the infecting organism, and prevent the emergence of resistance.
- Increasing the coverage of antimicrobial therapy is generally necessary in mixed infections in which multiple organisms are likely to be present, such as intra-abdominal and female pelvic infections in which a variety of aerobic and anaerobic bacteria may produce disease. Combination antimicrobial therapy is also used in critically ill patients with presumed healthcare-associated infections in which an increased spectrum of activity is desirable.

Synergism

- The achievement of synergistic antimicrobial activity is advantageous for infections caused by gram-negative bacilli in immunosuppressed patients.
- An example of synergy is the treatment of enterococcal endocarditis. The causative organism is usually only inhibited by penicillins, but it is killed rapidly by the addition of gentamicin or ceftriaxone to a penicillin.
- The use of combinations to prevent the emergence of resistance is widely applied but not often realized. The only circumstance in which this has been clearly effective is in the treatment of tuberculosis.

Disadvantages of Combination Therapy

- There are potential disadvantages from combining antimicrobials, including increased cost, greater risk of drug toxicity, and superinfection with even more resistant bacteria.
- Some combinations of antimicrobials are potentially antagonistic—for example, when one drug induces β-lactamase production and another

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drug is β-lactamase unstable.

MONITORING THERAPEUTIC RESPONSE

- After antimicrobial therapy has been instituted, the patient must be monitored carefully for a therapeutic response. Culture and susceptibility reports from specimens sent to the microbiology laboratory must be reviewed and the therapy changed accordingly.
- Use of agents with the narrowest spectrum of activity against identified pathogens is recommended.
- Patient monitoring should include a variety of parameters, including WBC count, body temperature, signs and symptoms of infection, appetite, radiologic studies as appropriate, and determination of antimicrobial concentrations in body fluids.
- As the patient improves, the route of antibiotic administration should be reevaluated. Transitioning therapy from parenteral to oral therapy should be encouraged when appropriate. Criteria favoring the switch to oral therapy include the following:
    - ✓ Overall clinical improvement
    - ✓ improvement in signs of inflammation (ie, down-trending fever curve and WBC)
    - ✓ A functioning gastrointestinal (GI) tract

FAILURE OF ANTIMICROBIAL THERAPY

- A variety of factors may be responsible for the apparent lack of response to therapy. It is possible that the disease is not infectious or nonbacterial in origin, or there is an undetected pathogen in a polymicrobial infection. Other factors include those directly related to drug selection, the host, or the pathogen. Laboratory error in identification and/or susceptibility testing errors are rare.

Failures Caused by Drug Selection

- Factors directly related to the drug selection include an inappropriate selection of drug, dosage, or route of administration. Malabsorption of a drug product due to GI disease (eg, short-bowel syndrome) or a drug interaction (eg, complexation of fluoroquinolones with multivalent cations resulting in reduced absorption) may lead to potentially subtherapeutic serum concentrations.
- Accelerated drug elimination is also a possible reason for failure and may occur in patients with cystic fibrosis or during pregnancy, when more rapid clearance or larger volumes of distribution may result in low serum concentrations, particularly for aminoglycosides.
- A common cause of failure of therapy is poor penetration into the site of infection. This is especially true for the so-called privileged sites, such as the CNS, the eye, and the prostate gland.

Failures Caused by Host Factors

- Patients who are immunosuppressed (eg, granulocytopenia from chemotherapy or HIV) may respond poorly to therapy because their own defenses are inadequate to eradicate the infection despite seemingly adequate drug regimens.
- Other host factors are related to the necessity for surgical drainage of abscesses or removal of foreign bodies and/or necrotic tissue. If these situations are not corrected, they result in persistent infection and, occasionally, bacteremia, despite adequate antimicrobial therapy.

Failures Caused by Microorganisms

- Factors related to the pathogen include the development of drug resistance during therapy. Primary resistance refers to the intrinsic resistance of the pathogens producing the infection. However, acquisition of resistance during treatment has become a major problem as well.
- The increase in resistance among pathogenic organisms is believed to be due, in large part, to continued overuse of antimicrobials in the community, as well as in hospitals, and the increasing prevalence of immunosuppressed patients receiving long-term suppressive antimicrobials

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for the prevention of infections.

See Chapter 132, Antimicrobial Regimen Selection, authored by Katie B. Olney and David S. Burgess, for a more detailed discussion of this topic

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